

### **REMARKS**

#### **Status of Claims and Amendment**

Upon entry of the Amendment, which is respectfully requested, claims 27, 31, 32, and 45 are all the pending claims in the present application. Claims 27 and 31 have been amended. Claims 1-26, 28-30, 33-44, and 46-51 have been canceled.

Claim 27 has been amended to incorporate the subject matter of claims 28 and 30. In addition, support for the amendments to claim 27 may be found at least in Example 2 of the specification.

Claim 31 has been amended to delete “gramicidin.”

No new matter has been added.

#### **Response To Claim Rejections Under 35 U.S.C. § 112**

1. Claims 27-29, 31, and 32 are rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite because the term “fresh” is unclear.

In response, Applicants submit that the claims prior to the present amendment clearly define what Applicants consider to be the claimed invention. However, solely to advance prosecution of the present application, “fresh” has been deleted from the claims.

Claims 28-29 have been canceled so that the rejection with regard to claims 28-29 is rendered moot.

Accordingly, reconsideration and withdrawal of the rejection under § 112, second paragraph, is respectfully requested.

2. Claims 27-29, 31, and 32 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

The Office Action asserts that the term “fresh” introduces new matter.

In response, and without conceding to the rejection, Applicants have deleted the term “fresh” from the claims solely to advance prosecution of the present application.

Accordingly, reconsideration and withdrawal of the rejection under § 112, first paragraph, is respectfully requested.

**Response To Claim Rejections Under 35 U.S.C. § 103**

Claims 27-29, 31, 32, and 45 are rejected under 35 U.S.C. § 103 as allegedly being unpatentable over El-Mallakh in light of Garrahan *et al.* “The Behavior of the Sodium Pump in Red Cells in the Absence of External Potassium,” *J. Physiol.* 192: 159-174 (1967) (“Garrahan”) or Antia *et al.* “The upregulation of Na<sup>+</sup>, K<sup>+</sup> -ATPase pump numbers in lymphocytes from the first degree unaffected relatives of patients with manic depressive psychosis in response to in vitro lithium and sodium ethacrylate,” *Journal of Affective Disorders*, 34: 33-39 (1995) (“Antia”).

It appears the Office Action has maintained the rejection for the reasons of record.

In addition, the Office Action asserts that the Rule 132 Declaration submitted in the Amendment filed August 31, 2007, was insufficient to overcome the rejection because the although the evidence provided is credible, the claimed method and the documents cited by the Office Action are based on the ratio obtainable from the various measurements under various different conditions. The Office Action contends that it would have been obvious for one of

ordinary skill in the art to measure membrane potentials of cells under difference combinations of parameters and “pick and choose” the measured membrane potential to obtain a meaningful ratio between control and bipolar patients. (See paragraph bridging pages 2-3 of the Office Action).

In addition, the Office Action asserts that because Buss et al. teach that there is no significant difference between normal and bipolar patients, and the method of Buss is similar to the method of El-Mallakh, the results of Buss “would not reasonably allow [one of ordinary skill in the art] to expect that the measurement of membrane potential ratio disclosed in the [Rule 132] [D]eclaration would differentiate between normal vs. bipolar disorder.” (See page 3, lines 7-13 of the Office Action).

Applicants note that pursuant to the M.P.E.P. §2143.02, the “prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success”, and “[e]vidence showing there is no reasonable expectation of success may support a conclusion of nonobviousness.”

In this regard, Applicants note that the documents cited by the Office Action and the above statements by the Office supports Applicants’ position that 1) the present method provides unexpected results that were not obvious to one of ordinary skill in the art at the time the invention was made, and 2) that based upon the teachings of the documents cited by the Office, one of ordinary skill in the art had no reasonable expectation of success to support a *prima facie* case of obviousness because there would have been no reason or suggestion to combine the cited documents. However, even if one of ordinary skill in the art was, somehow motivated to

combine the teachings of the cited documents, one of ordinary skill in the art would not have obtained Applicants' unexpected results because none of the cited documents would have suggested or given one of ordinary skill in the art a reason to use K<sup>+</sup>-free buffer and the absence of a potential-sensitive dye when measuring cell fluorescence, as required in the presently claimed method.

Further, Applicants note that the Office's mere combination of known prior art elements is not sufficient to render the claimed invention obvious if the results would not have been predictable to one of ordinary skill in the art [emphasis added]. United States v. Adams, 383 U.S. 39, 51-52 (1966). Furthermore, there must be some teaching, suggestion, or motivation that would have led one of ordinary skill in the art to modify the reference teachings, or to combine the reference teachings to arrive at the claimed invention. M.P.E.P. §2143.01. The mere fact that the references can be combined or modified is not sufficient to establish a *prima facie* case of obviousness unless the references also suggests the desirability of the combination. Id. Accordingly, a *prima facie* case of obviousness may be rebutted by evidence showing unpredictable or unexpected results. KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727 (2007).

In the present case, and as stated by the Office Action, the "data presented in the declaration may be unexpected under the assumption that such comparison would produce any significant difference between normal and affected subject[s]." (See page 3, 1<sup>st</sup> sentence of the Office Action). Applicants note that the previous Rule 132 Declaration and the Supplemental Rule 132 Declaration submitted herewith provide evidentiary data to demonstrate and support

that Applicants' presently claimed method provides unexpected results that significantly differentiate between the membrane potentials of control and bipolar individuals to diagnose bipolar disorder in a human patient. The fact that prior investigators have been unable to achieve the results obtained by Applicants only further supports Applicants' position that one of ordinary skill in the art, even with knowledge gleaned from the combined teachings of the cited documents, would not have obtained Applicants' claimed invention, nor would one of ordinary skill in the art have had a reasonable expectation of success in obtaining Applicants' claimed invention.

Further, Applicants note that to establish a *prima facie* case of obviousness, "the prior art reference (or references when combined) must teach or suggest all the claim limitations". M.P.E.P. §2143. Applicants note that none of the cited documents teach or suggest the use of K<sup>+</sup>-free buffer, and the absence of a potential-sensitive dye when measuring cell fluorescence as required in the presently claimed method.

Moreover, as acknowledged by the Office Action at page 6, 1<sup>st</sup> full paragraph, "El-Mallakh...[does] not teach the use of various combination of presence or absence of potassium during the measurement", and the sentence bridging pages 6-7, "El-Mallakh...[does] not teach the use of ethacrynate."

Thus, for at least the reasons discussed above and the reasons presented in the Amendments filed August 31, 2007, and March 2, 2007, the presently claimed method would not have been obvious to one of ordinary skill in the art at the time the invention was made.

AMENDMENT UNDER 37 C.F.R. § 1.114(c)  
U.S. Application No.: 10/823,647

Attorney Docket No.: A8709

Accordingly, reconsideration and withdrawal of the rejection under § 103(a) is respectfully requested.

**Conclusion**

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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